Ovarian Hyperstimulation Syndrome (OHSS) Caused by Fertility Treatment [1]

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Ovarian hyperstimulation syndrome, abbreviated OHSS, is an atypical reaction that women may experience in response to excessive hormones [9], and often occurs during fertility treatments. OHSS is typically triggered by hormonal medications designed to mature eggs in the ovaries, which can cause blood vessels within the ovaries to leak fluid. Sometimes that can lead to painful tenderness or swelling. In severe cases of OHSS, that fluid can leak into the abdominal cavity in large amounts, causing vomiting, blood clots, and severe pain. As many as one out of three women undergoing fertility treatment will experience some form of OHSS, although more severe presentations are rare. While the exact cause of OHSS is not fully understood as of 2020, researchers continue to discover various risk factors, prevention techniques, and treatments that may lead to decreased risks associated with OHSS and better fertility outcomes.

OHSS is a condition that affects the endocrine system, which consists of endocrine glands that secrete chemical messengers called hormones [8] to regulate the body’s activities. Gonads, a type of endocrine gland that includes the testes [6] and ovaries, are regulated by gonadotropic hormones [8], also known as gonadotropins. During pregnancy [7], once a fertilized embryo attaches itself to the uterine lining, the body produces a type of gonadotropic hormone [10] called human chorionic gonadotropin [9], or hCG. For women undergoing fertility treatment such as in vitro [10] fertilization [11], or IVF, a healthcare professional may inject them with hCG shots in order to trigger ovulation [12], which is the release of mature eggs from the ovaries. During IVF treatment, hCG shots are often necessary because sperm [13] cannot fertilize immature eggs. Researchers have found that OHSS can sometimes occur after the administration of hCG injections, although researchers suspect there are likely other reasons contributing to its occurrence.

In the early twentieth century, researchers began experimenting with gonadotropins such as hCG for its potential use as a fertility medication. At that time, scientists also documented some of the earliest known cases of OHSS. In 1927, two researchers from Germany named Selmar Aschheim [14] and Bernhard Zondek [15], found that the urine and blood of pregnant women contained what is now recognized as hCG. Other scientists later studied different forms of gonadotropins, such as pregnant mare serum gonadotropin [16], or PMSG, in addition to hCG for clinical use in humans [17]. In the 1940s, researchers began observing OHSS incidentally after conducting research on those gonadotropins and their interaction with human ovaries. According to researchers Annick Delvigne and Serge Rozenberg, scientists first formally recognized OHSS in 1943. Other researchers published some of the first cases of death due to the syndrome in 1951, as well as some of the first cases that required surgical removal of the ovaries in 1957.

Awareness of OHSS has increased over time due to the increased popularity of fertility treatments such as IVF. As a result, the amount of women who have experienced some form of OHSS has also increased over time. In 1958, researchers documented one of the first successful pregnancy [7] inductions in a woman with the administration of hCG and other gonadotropins. Up until 1961, researchers had only recorded about sixty cases of OHSS as a result of treatment to induce ovulation [12] with hormones [8]. In 1963, one group of researchers observed women experiencing symptoms of OHSS in four out of twenty-two treatments. However, after that group of researchers changed their procedure to track sex hormones [18] in their patients during treatment, the researchers observed only one case of OHSS in 1970. With the development of IVF in 1978, and techniques such as cryopreservation [19], OHSS rates began to increase as physicians tried progressively zealous treatment experiments in order to harvest large numbers of eggs so that the success rates of fertility treatments increased. Since the 1980s, researchers have continued to work towards determining the causes of OHSS, risk factors, prevention techniques, and pregnancy [7] outcomes after OHSS.

According to the Mayo Clinic, although physicians do not understand the exact causes of OHSS, they generally agree that high levels of hCG can cause the ovarian blood vessels to leak fluid. That excessive fluid can be particularly damaging to the kidneys and may aid in the formation of blood clots. Those blood clots can travel to the lungs or other important organs where they can cause serious effects, such as strokes or heart attacks. While researchers recognize the role of hCG in the development of OHSS, it is not the only hormone [8] that may cause women to experience the syndrome. In the past, researchers have investigated the role of estradiol [20], an estrogen [21] steroid hormone [8] that scientists sometimes administered prior to hCG injection, as a cause of OHSS. Additionally, researchers have monitored and analyzed blood samples for certain chemicals released by a woman’s immune system during fertility treatments to see whether there was a marked increase or decrease that could explain the syndrome. However, despite those studies, researchers generally agree that the exact mechanism behind OHSS is still unclear.

There are two types of OHSS, early onset and late onset, which can both result in varying degrees of severity. Early onset
OHSS occurs within days after inducing ovulation\textsuperscript{[12]}, while late onset OHSS typically occurs ten or more days after inducing ovulation\textsuperscript{[12]}. Physicians associate early onset OHSS with higher rates of pregnancy\textsuperscript{[7]} loss before seven weeks of gestation\textsuperscript{[22]} among women undergoing IVF. Late onset OHSS, which is more likely to cause serious symptoms than early onset OHSS, is mainly caused by hCG released from the placenta\textsuperscript{[23]} and usually only occurs in women who become pregnant as a result of IVF treatment. Approximately one out of three women undergoing IVF treatment may experience symptoms with mild OHSS that include nausea, abdominal bloating, abdominal discomfort, and diarrhea. Around 5 percent of women undergoing ovarian stimulation experience a moderate case of OHSS, which is characterized by a worsening of those same symptoms seen in women with mild OHSS. Severe OHSS occurs in less than 2 percent of women undergoing ovarian stimulation, and is characterized by severe pain, persistent nausea and vomiting, rapid weight gain caused by fluid accumulation, blood clots, and shortness of breath. Mortality estimations due to OHSS vary widely from country to country. Whereas some sources estimate three out of every 100,000 women undergoing ovarian stimulation may die from severe OHSS, others report that the rate may be closer to one out of every 500,000 women.

Physicians have identified certain risk factors for OHSS, as well as preventative measures that can be taken in order to avoid OHSS in higher risk groups. Although some women with no risk factors can develop OHSS, a woman is more likely to develop OHSS if she has had it before, has a low body weight, or is younger than thirty-five years old. Additionally, a woman is more likely to develop OHSS if she either has high levels of estrogen\textsuperscript{[25]} before hCG injection, or has polycystic ovarian syndrome, a relatively common reproductive condition that results in irregular periods, excessive hair growth, and enlarged polycystic ovaries. Women who exhibit any of those risk factors may require scientists to take extra precautions during fertility treatment. Because hCG is a known trigger for OHSS, physicians may choose to either administer the lowest effective dosage of hCG that will still result in inducing ovulation\textsuperscript{[12]}, or to avoid administering hCG altogether and move on to alternative hormone\textsuperscript{[8]} therapies. Physicians may also choose to utilize the prevention technique known as coasting, which is when the fertility specialist delays the hCG shot until the woman’s estradiol\textsuperscript{[20]} levels have reached a level deemed safe enough that the risk of OHSS decreases. Additionally, women who have experienced OHSS in the past may choose other preventative methods, move on to alternative fertility options, or decide to freeze their eggs and resume IVF at a later point in their lives.

If a woman develops OHSS, physicians may use a range of options to monitor and treat women until the condition resolves. Mild OHSS, the most common form that may affect up to one out of three women undergoing ovarian stimulation, typically does not require any treatment and may in many cases resolve within a week. In cases with moderate OHSS, a physician may advise their patient to avoid any strenuous activities, as well as possibly monitor fluid intake and output to determine whether she is retaining fluid in her abdomen. If an IVF cycle is successful at inducing pregnancy\textsuperscript{[7]}, it can potentially aggravate moderate OHSS due to the subsequent release of hCG that is naturally secreted from placental tissue, which develops shortly after an embryo implants into the uterus\textsuperscript{[24]}. Women with severe OHSS may require hospitalization, where doctors monitor those patients closely and observe for any additional complications. Such observation may involve vaginal ultrasound\textsuperscript{[25]} and blood tests to check the health of a woman’s ovaries and kidneys. Additionally, doctors might prescribe medications to remove fluid from the abdomen, or manually drain fluid from the abdomen using a syringe.

The scientific community has debated whether certain methods of OHSS prevention are effective, as well as possible effects of OHSS prevention on pregnancy\textsuperscript{[7]} outcomes. In one review study conducted in 2010 in São Paulo, Brazil, researchers found that the coasting effect still does not present sufficient evidence to support its use for preventing OHSS. They concluded that the safest way of preventing OHSS is through the use of in vitro\textsuperscript{[10]} maturation, or IVM, of a woman’s eggs. IVM is when physicians collect immature eggs from unstimulated ovaries, meaning that added hormones\textsuperscript{[9]} are not required to induce ovulation\textsuperscript{[12]}. However, IVM may result in less successful rates of implantation\textsuperscript{[26]}, the attachment of the embryo to the uterus\textsuperscript{[22]}, and less successful pregnancy\textsuperscript{[7]} rates than standard IVF with the use of hCG. Generally, researchers tend to agree that a reduced dosage of hCG in higher risk groups seems to lower rates of OHSS without many significant drawbacks.

For women who develop OHSS, the effects of OHSS on pregnancy\textsuperscript{[7]} outcomes are ambiguous due to a lack of large-scale research studies. In one study, researchers from the Center for Reproductive Medicine in Brussels, Belgium, included 113 pregnant women who were hospitalized with severe OHSS following IVF treatment. From their investigation, the researchers found that although women with early OHSS were more likely to suffer from miscarriage\textsuperscript{[27]} prior to week seven of gestation\textsuperscript{[22]}; women with late OHSS were more likely to have multiple pregnancies such as twins or triplets. That may be due to the fact that pregnancies with multiple fetuses tend to result in higher levels of natural hCG secretion. Despite those findings, many additional smaller studies seem to indicate that there is no statistically significant difference in miscarriage\textsuperscript{[27]} rates between women with and without OHSS. Scientists have called for additional large-scale research studies to determine how OHSS affects pregnancy\textsuperscript{[7]} outcomes in women undergoing IVF treatment.

Sources

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